The statutory provision in question requires that the application provide a written description of the invention which is sufficient to enable any person skilled in the art to make and use the invention. Applicants respectfully submit that the disclosure of the present invention is clearly sufficient to enable the art-skilled to make the compositions of the invention and to use such compositions to the full scope of the subject matter being claimed.

The Examiner states that the specification is enabling only for those ratios which have been demonstrated to be synergistic. The Applicants completely disagree with the position advanced by the Examiner and do not understand how the Examiner can properly take such position. There is no reason to believe that the art-skilled, based upon the disclosure of the present application, would be able only to make and use those compositions which are specifically demonstrated to be synergistic. Applicants submit that this is not at all the case and that these specific compositions are purely illustrative and not exhaustive of the subject matter of the present invention. Those skilled in the art could, based upon the disclosure of the present application, readily make and use other specific compositions within the scope of the claimed subject matter and which are synergistic.

The Examiner is thus respectfully requested to reconsider and withdraw the objection to the specification and the rejection of the claims.

The claims are rejected under the provisions of 35 U.S.C. 103 as being unpatentable over Deng (AQ) in view of Wang et al. (R) and Lin et al. (S). This ground of rejection is deemed to be untenable and is thus respectfully traversed.

The Deng and Wang et al. references have been discussed in great detail in the previous prosecution of the present application and Applicants' position in respect to the teachings of those references has been set forth in detail. Particular attention is directed to Applicants' response of January 17, 1995. Applicants' comments concerning these references are thus incorporated herein by reference.

The Lin et al. reference is newly cited by the Examiner and does, of course, require specific consideration.

In arguments previously presented by Applicants, it has been emphasized that prior to the present invention, the oral administration of artemether was not known and was not obvious to one of ordinary skill in the art within the meaning of 35 U.S.C. 103. In countering Applicants' arguments, the Examiner has cited the Lin et al. reference and urges that the reference teaches artemether as an antimalarial agent which is administered orally. Applicants respectfully submit that when the teachings of the Lin et al. reference are considered in detail, the Applicants' arguments remain valid and that the Lin et al. reference does not in any way detract from the patentability of the instantly claimed subject matter.

First, it is to be pointed out that Applicants have established previously on the record that artemether was, at the time of the present invention, recognized as being unsuitable for formulation in an oral dosage form. This can be explained by the low solubility and weak gastrointestinal absorption of the active agent. Thus, the information that artemether is administered orally, as appears at first glance to be reported in the newly cited Lin et al. reference, therefore appears rather surprising and would stimulate the

interest of those skilled in the art. To obtain further information, the art-skilled would then have taken a closer look into the complete Lin et al. publication. Upon doing so, he would, however, discover that the abstract appearing in the Chemical Abstracts reference cited by the Examiner incorrectly reports the contents of the Chinese publication. The term "oral" has erroneously - in the abstract - been assigned to a type of administration which is, in reality, intragastric. The intragastric administration of an active agent to animals is unrelated with any oral dosage form containing the same agent. It can, therefore, be concluded that the newly cited reference of the Examiner does not, in fact, suggest what it *prima facie* appears to suggest.

The Examiner is presently contending that the oral administration of artemether to animals as mentioned in the newly cited Lin et al. reference, would suggest an oral dosage form, such as tablets, administered to humans. Without any doubt, "orally" is mentioned as a key term in the Chemical Abstracts publication. However, in the English translation of the Chinese reference which is attached hereto, this term is not mentioned at all. As is apparent in the English translation which is attached, the publication only mentions "intragastric gavage" of the active agent. In this respect, see the attached English translation, page 1, the second full paragraph.

The terms "orally" and "intragastric gavage" are certainly not synonymous. There are some remarkable differences between these modes of administration. According to Webster's New Universal Unabridged Dictionary, second edition, 1983, page 759 (copy attached) "gavage" is defined as:

forced feeding of poultry through a tube for the purpose of fattening them for market
as to human administration: a similar method of giving nourishment to a patient.

The differences between both modes of administration is self-evident. The Chinese publication teaches only the forced administration of a substance to animals through a device such as a tube. It does not teach oral administration through the mouth. Intragastric administration is typical of animal experimentation and deemed to be clearly distinct from the self-administration of a conventional oral dosage form, such as a tablet, to human beings. The term "orally" as mentioned in the Chemical Abstracts publication, therefore appears incorrectly chosen for defining the type of administration that was actually carried out according to the Lin et al. publication. This reference should, therefore, be interpreted differently in light of the complete Chinese publication. It follows therefore that Lin et al. is, in reality, further away from the claimed subject matter than appears from a literal interpretation of the Chemical Abstracts publication.

It is additionally to be pointed out that even if the Chemical Abstracts publication itself should be interpreted without referring to the translation of the original Lin et al. Chinese publication, such publication does not suggest an oral dosage form. The point to be made here is that the oral administration of an active agent to animals does not suggest an oral dosage form of the active agent.

In view of the enormous number of publications that appear daily, the art-skilled are unable to evaluate - let alone translate - thoroughly each publication which is summarized by abstracting in Chemical Abstracts. It has become common daily practice that those skilled in the art only rely on the short

abstracts which are published without further control of the complete publications and the correctness of the abstract. Therefore, the art-skilled might consider only what the isolated Chemical Abstracts publication would teach without relying upon the specific information from the complete Chinese publication. Thus, the artisan might view the isolated Chemical Abstracts publication literally to the effect that artemether is administered orally to animals. However, any *prima facie* assumption that such literal interpretation would teach an oral dosage form administered to humans is completely incorrect.

Pharmacological activity and toxicological studies of new compounds with animals as required by the World Health Organization (WHO) or national regulatory authority, e.g., the U.S. Food & Drug Administration (FDA), routinely comprise various routes of administration. In this respect, see Principles for Pre-Clinical Testing of Drug Safety, WHO Technical Report Series No. 341 (1966), page 7 (attached hereto). This publication states:

> "Typical experiments on new drugs involve the administration of single doses by various routes to animals and measurement of drug concentrations in body fluids and tissues."

According to the Guidelines for the Format and Content of the Non-Clinical Pharmacology/Toxicology Section of an Application (see attached), the oral route is recommended but also other routes of administration. Those documents clearly show that there is no direct link between the route of administration chosen for conducting animal experiments and the type of dosage form developed for administering the same agent to humans.

In addition, there are further reasons why the animal experiments, as reported in the Chemical Abstracts publication, do not suggest an oral dosage form.

In animal experimentation, two different modes are used for administering compounds to rodents when testing the absorption in the gastrointestinal tract:

(a) Food pellets which contain measured amounts of the drug to be tested. By feeding the pellets when the animals are hungry, their intake is ensured. Pellets are used as vehicles for the oral administration of drugs presenting no problems regarding solubility, dispersibility or taste. This method may be defined as oral administration.

(b) Intragastric (i.g.) gavage with drug solutions or suspensions. This method is primarily employed for administering higher doses of poorly water-soluble compounds.

The dose of 100 to 200 mg/kg/day, administered up to seven days to small mice, appears very high and reveals toxicologic experimentation. The Chemical Abstracts publication mentions a "markedly enlarged spleen". This points to toxicity effects caused by the high dosage administered rather than to immunological effects. To administer an almost insoluble active agent at an extremely high dose, anyone skilled in the art would reject method (a) of administering the active agent orally with food pellets and would, rather select the (i.g.) method (b). The English translation of the Chinese publication reveals that a 1% aqueous suspension of tragacanth gum was administered via the i.g. route. Therefore, the abstract contains a contradiction between the high dose chosen and the alleged oral administration. When high doses are administered, they are not administered orally.

Applicants further respectfully submit that the combination of the new Lin et al. reference with the other references previously cited and relied upon by the Examiner, does not suggest the claimed dosage form containing the active agents.

Applicants have explained above that the newly cited Lin et al. reference does not suggest an oral dosage form containing artemether. This allows the reasonable conclusion that the combination of the new reference with the other references previously cited and relied upon by the Examiner also does not suggest an oral dosage form containing the combined active agents benflumetol and artemether.

Based upon the foregoing remarks, Applicants respectfully submit that the Examiner's rejection of the claims as lacking patentability under the provisions of 35 U.S.C. 103 over the teachings of the cited references is untenable and should be reconsidered and withdrawn.

It is respectfully submitted that the present application is now in condition for allowance and such allowance is solicited.

Respectfully submitted,

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(1)

C.A. 103:134524 Yaoxue Xuebao (1985), 20(3), 211-213 Engl.Translation

The effects of artemether on serum IgG and spleen weight in mice

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Some immunological effects of artemisinin and sodium artesunate had been already reported (1—3). Employing single radial immunodiffusion test (4), this article estimated the effect of oral artemether administration on serum IgG and spleen weight in mice.

Inbred JCR mice of 20 — 25g body weight were used. Mice of both sexes (equal number) were randomly divided into groups. Artemether (Kweilin Pharmaceutical Factory) and chloroquine (Chung — kung Pharmaceutical Factory) were suspended in 1% gummi tragacanthae for intragastric gavage. Rabbit anti mouse IgG antiserum, standard JCR mouse serum antigen were prepared by the laboratory (4).

1. The effect of artemether on serum IgG in normal mice

Seventy nine mice were grouped randomly into artemether high dose group (200mg/kg/d), low dose group (100mg/kg/d), chloroquine group (200mg/kg/d) and control. To treated groups drugs were given twice daily for 7 days. Same amount of gummi tragacanthae was given to controls. Twenty four hours after the last medication, took orbital blood from every groups, collected the serum and measured the serum IgG of each mouse using single radial immunodiffusion test. The experiments were carried out twice. Results showed that mean IgG value of control was 12.56 ± 0.72mg/ml ($\bar{X} \pm SE$); high dose artemether group 8.82 ± 0.73mg/ml, in comparison with that of control, the difference was highly significant ($P < 0.001$). It indicated that artemether (200mg/kg/d) reduced markedly the serum IgG in

normal mice, while chloroquine exhibited no evident effect on the serum IgG in normal mice.

2. The effect of artemether on serum IgG in SRBC immunized mice

The experimental conditions were essentially the same as above mentioned, the only difference was that on the 2nd day after medication, 71 mice were immunized by ip 0. 2ml antigen (20% SRBC suspension, SRBC 2 $\times 10^8$/ml) individually. Results of doubly repeated experiments showed that the IgG value of control was 14. 62 $\pm$ 0. 70mg/ml and of low dose artemether group 12. 20 $\pm$ 0. 74mg/ml. The difference between two groups was significant ($P < 0.05$), it pointed out that artemether (100mg/kg/d) decreased the serum IgG of immunized mice, while chloroquine showed no such effect.

3. The effect of artemether on serum IgG in plasmodium berghei infected mice

By routine method (5), 77 normal mice were infected with plasmodium berghei. After parasite inoculation mice were divided randomly into high dose artemether group (200mg/kg/d), low dose artemether group (100mg/kg/d) and infected control. Medication initiated 24h after inoculation twice daily for 4 days. Same amount of gummi tragacanthae was given to control. 24h after the last medication made thin smears, stained and examined microscopically to observe the parasite clearance or infection rate, collected the serum and estimated the serum IgG by single radial immunodiffusion test. Results of doubly repeated experiments showed that the parasite suppression rate of 2 dose groups of artemether and chloroquine were 100%. No difference in serum IgG existed between 2 dose groups of artemether and chloroquine treated group in comparison with infected control group ($P > 0.$

05).

4. The effect of artemether on spleen weight

Experimental conditions were the same as those mentioned above. 24h after last medication, orbital blood was taken and mice sacrificed, took and weighed spleen, then calculated the spleen weight per 10g body weight. Results pointed out: the difference in spleen weight between 2 dose groups of artemether and controls was highly significant ($P < 0.01 - 0.001$). It reflected that artemether could increase the spleen weight of normal mice while chloroquine could not. Furthermore, 2 dose levels of artemether could also increase the spleen weight in SRBC immunized mice. In comparison with that of control, the difference was highly significant ($P < 0.001$). Chloroquine had no such effect.

Experimental results also demonstrated that the spleen weight of Plasmodium berghei infected mice treated by 2 dose levels of artemether was much lower than that of untreated, infected mice. No malaria parasite was detected in the blood of artemether treated mice, it indicated that antimalaria efficacy of artemether might prevent the increse of spleen weight. The spleen weight of chloroquine treated group decreased also in comparison with infected control group.

Discussion

The results of the experiment in this article showed that artemether could reduce not only the serum IgG of normal mice but also that of SRBC antigen stimulated mice, it indicated that artemether exhibited suppressive effect on humoral immunity. Besides, artemether increased the spleen weight of both normal and SRBC antigen stimulated mice. The change of spleen (an

immune organ) weight might reflect the magnititude of proliferation of immunocytes and the change of immunological function of the organism. From the results, the authors deduced that artemether might act to promote the proliferation of the spleen T_s cells, consequently suppress the IgG. It provided the basis for extending the clinical application of artemether. The effect of artemether on serum IgG and spleen was quite similar to those characteristics exhibited by artemisinin. Artemisinin had been reported to have satisfactory therapeutic efficacy in the treatment of lupus erythematosus (6). The authors considered that artemether might be also used in the treatment of lupus erythematosus and immune disease in clinics. Besides, in the parallel control study with chloroquine, the authors note that under the dose used in the study, chloroquine reduced the spleen weight of malarial mice, and had no effect on serum IgG and spleen weight in normal and SRBC sensitized mice, this fact demonstrated that the pharmacological action of artemether was different from that of chloroquine. For evaluating rationally the drug action, the author designed to study the immune effect of artemether at different dose levels in mice. Results pointed out that the effect of different doses of artemether on serum IgG in mice was different, whereas the effect of the same artemether dose on serum IgG in different status of mice was also different. High dose artemether (200mg/kg/d) could markedly lower the serum IgG in normal mice, while low dose (100mg/kg/d) had no such effect. On the contrary, low dose reduced serum IgG markedly in SRBC immunized mice, while high dose not. This phenomenon explained that different doses could alternate the effect of artemether on serum IgG level in mice and the susceptibility of organism to artemether under different status was also different. From the standpoint of immunology, it provided the evidence of considering the patient's immune status in clinical artemether medication.

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gauging

beam end of a plow to regulate the depth of the furrow.

gau'ging, *n.* the art or method of determining the dimensions or capacity of anything.

Gaul, *n.* [OFr. *Gaule*; L. *Gallus*; Gr. *Gallos*.]
1. any of the Celtic-speaking people of ancient Gaul.
2. a Frenchman.

Gau'lei-tĕr (gou'lī-tĕr), *n.* [G.] a district leader or administrator under the Nazi regime.

Gaul'ish, *a.* pertaining to Gaul or the Gauls.

Gaul'ish, *n.* the continental branch of the Celtic languages, spoken in ancient Gaul.

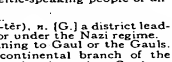
Gaul-thĕ'ri-a, *n.* a genus of shrubs of the heath family, of which the American wintergreen, *Gaultheria procumbens*, is typical, having evergreen leaves and red, edible berries: named after Dr. Gaultier, a Canadian physician; also, [g—] any plant of this genus.

gaum, *v.t.* [Prov. Eng., from AS. *gyman*, *giman* to care for, heed.] to understand. [Brit. Dial.]

gaum, *v.t.* to daub or smear. [Brit. Dial.]

gaunt, *a.* [ME. *gaunt*, *gaunte*, lean, slender; prob. from Norw. *gand*, a thin pole.]
1. thin and bony; emaciated; hollow-eyed and haggard, as from great hunger or age.
2. looking grim, forbidding, or desolate.

gaunt'let, gânt'let, *n.* [OFr. *gantelet*, dim. of *gant*, a glove, from D. *want*, a mitten.]
1. a glove; specifically, in medieval armor, the defensive covering of the hand and wrist.


GAUNTLETS

2. a long glove with a flaring cuff covering the lower part of the arm.
3. the part of such a glove covering the lower part of the arm.
4. in surgery, a form of bandage for the hand.
to take up the gauntlet; (a) to accept a challenge; (b) to undertake the defense of a person, etc.
to throw down the gauntlet; to challenge.

gaunt'let, *n.* a gantlet (form of punishment).

gaunt'let-ed, *a.* having or wearing a gauntlet, or glove.

gaunt'ly, *adv.* leanly; meagerly.

gaun'try, *n.*; *pl.* **gaun'tries,** a gantry.

gaur, gour, *n.* [native E. Ind. name, from Sans. *gaura*, a wild ox.] an East Indian variety of wild cattle similar to the domesticated gayal.

gaure, *v.i.* to gape; to stare; to gaze with open mouth. [Obs.]

gauss, *n.* [after Karl F. *Gauss* (1777–1855), G. mathematician and physicist.] in electricity, a unit used in measuring magnetic induction or magnetic intensity, equal to one linc of magnetic force per square centimeter.

Gauss'i-ăn, *a.* named after or discovered by Karl F. Gauss; as, *Gaussian* logarithms.

gauze, *n.* [Fr. *gaze*, gauze, said to be from *Gaza*, in Palestine, where it was first made.]
1. a very thin, light, loosely woven material, usually of silk or cotton: also applied to other material of similar open texture; as, wire *gauze*.
2. a thin mist or haze.

gauze, *a.* made of or like gauze; gauzy.

gauze tree, the lacebark tree, *Lagetta lintearia*, of the West Indies.

gauz'i-ness, *n.* the quality of being gauzy.

gauz'y, *a.*; *comp.* gauzier; *superl.* gauziest; thin, light, and transparent, like gauze; diaphanous.

ga-vage' (-väzh'), *n.* [Fr., from *gaver*, to gorge fowls with food in order to fatten them, from *gave*, the crop or craw of a bird.]
1. forced feeding of poultry through a tube, for the purpose of fattening them for market.
2. a similar method of giving nourishment to a patient.

gâve, *v.* past tense of *give*.

gav'el, *v.t.*; gaveled, *pt., pp.*; gaveling, *ppr.* to distribute equally, according to the tenure of gavelkind.

gav'el, *n.* [ME. *gavel*; AS. *gafol*, tribute, tax.] tribute. [Obs.]

gav'el, *n.* [OFr. *gavelle*, a sheaf of corn.] a small unbound parcel of wheat, rye, or other grain, laid together by reapers. [Brit. Dial.]

gav'el, *n.* a gable. [Brit. Dial.]

gav'el, *n.* [use only in U. S. suggests D. or dial. G. origin.]
1. a mason's hammer for breaking off the rough edges of stones.
2. a small mallet rapped on the table by a presiding officer in calling for attention or silence.

gav'el-et, *n.* [from ME. *gavel*; AS. *gafol*, tribute, tax,] in English law, a special writ used for the forfeiture of property because of the withholding of rent or services. [Obs.]

gav'el-kind, *n.* [ME. *gavelkynde*, *gavelkende* (orig. Kentish), from *gavel*, tribute, tax, rent, and *kynde*, *kinde*, kind, sort.]
1. formerly, a system of land tenure by which: (a) the property of a man dying intestate was divided equally among his sons; (b) the tenant could dispose of his land by feoffment at the age of fifteen; (c) the land did not escheat upon the conviction of the tenant as a felon.
2. a similar system of land tenure still practiced in Kent and Wales.

gav'e-lock, gav'e-loche, *n.* [ME. *gavelock*; AS. *gafeluc*, a spear or javelin.]
1. a dart; a spear. [Obs.]
2. an iron lever; a crowbar. [Obs.]

gă'vĕr-lick, *n.* the red gurnard, a kind of fish.

Gă'vi-ae, *n.pl.* [L. *gavia*, a sea mew.] a group of birds of which gulls are the type.

gă'vi-ăl, *n.* [Hind. *ghariyāl*, a crocodile.] a large Indian crocodile, *Gavialis gangeticus*, having a long, slender snout with a knob on the upper jaw: found chiefly in the Ganges.

Gă-vi-al'i-dae, *n.pl.* a family of crocodiles of which the gavial is the type.

gă-votte', gă-vot', *n.* [Fr. *gavotte*; OFr. *gavote*, a dance of the *Gavots*, name of people of Hautes-Alpes, France, where the dance originated.] a seventeenth-century dance like the minuet, but faster and livelier; also, the music for this.

gaw, *n.* a ditch or trench. [Scot.]

Gă'waln (-win), *n.* [prob. from W. *Gwalchmai*; perh. lit., courteous.] in Arthurian legend, a knight of the Round Table, nephew of King Arthur.

gawk, *n.* [ME. *gowke*, a cuckoo, a fool; Ice. *gaukr*, cuckoo.] a simpleton; a clumsy, stupid fellow.

gawk, *v.i.* gawked, *pt., pp.*; gawking, *ppr.* to stare like a gawk, in a stupid way. [Colloq.]

gawk'i-ly, *adv.* in a gawky manner.

gawk'i-ness, *n.* the quality of being gawky.

gawk'y, *n.* an awkward, ungainly, or stupid fellow.

gawk'y, *a.* foolish; awkward; clumsy; clownish; ungainly; uncouth.

gāy, *a.* [ME. *gay*; OFr. *gai*; O.H.G. *gahi*, quick, sudden, rash, lively.]
1. joyous and lively; merry; happy; light-hearted.
2. bright; brilliant; as, *gay* colors.
3. given to social life and pleasures; as, a *gay* life.
4. wanton; licentious; as, a *gay* dog.
5. homosexual.
Syn.—merry, lively, blithe, sprightly, sportive, hilarious.

gāy, *n.* a homosexual; especially, a male homosexual.

gāy'al (gā'āl), *n.* [native E. Ind. name.] a species of ox, *Bos frontalis*, found wild in the mountains of northern Burma and Assam, and domesticated in these countries and in the eastern parts of Bengal.

Gā-yā-trī', *n.* [Sans.] a Sanskrit hymn used in the Hindu liturgy.

gāy'bine, *n.* any one of several showy twining plants of the genus *Ipomœa*.

gay'dl-ang, *n.* [native Annamese.] a vessel of Annam with curved decks, somewhat resembling a Chinese junk, and carrying two or three masts and large, triangular sails.

gāy'ĕ-ty, *n.* same as *gaiety*.

gāy'-feath"ĕr (-feth"), *n.* the button snakeroot, *Liatris spicata*.

Gāy"lus-sā'ci-a (-shi-), *n.* [after Joseph *Gay-Lussac*, early 19th-c. French scientist.] a genus of ericaceous shrubs, some deciduous and others evergreen. They have clusters of white or pink green flowers, and black or blue edible fruit, commonly known as huckleberries. They are found in the eastern sections of both North and South America. The common or black huckleberry is the fruit of *Gaylussacia resinosa*.

gāy'lus-site, *n.* [after *Gay-Lussac*; see prec. entry.] a white, brittle, glassy sodium-calcium carbonate, found in Peru and in Nevada.

gāy'ly, *adv.* same as *gaily*.

gāy'ness, *n.* gaiety.

Gāy"-Pāy'-Oō', [from first letters of Russ. *Gosudarstvennoye Politicheskoye Upravlyenive*, governmental political department.] formerly, the state security police, or secret service, of the Soviet Union, succeeding the Cheka in 1922.

gāy'sŏme, *a.* full of gaiety.

gāy'wings, *n.* a bruising pink wildflower of the eastern United States and Canada.

gāy'you, *n.* [Anglo-Ind.] a narrow, flat-bottomed Annamese fishing boat. It has an outrigger and either two or three masts, and is provided with a movable roof amidships.


GAYYOU

Gā-zā'ni-ā, *n.* a genus of herbs of the aster family, characterized by large, showy, orange and yellow blossoms, which expand only in bright sunshine. They are native to South Africa and are named after Theodorus Gaza, a medieval Greek scholar of Italy.

gāze, *v.i.*; gazed, *pt., pp.*; gazing, *ppr.* [ME. *gasen*, from Sw. dial. *gasa*, to gaze, stare.] to fix the eyes and look steadily and earnestly; to look with eagerness or curiosity, as in admiration, astonishment, expectancy, or study.
Ye men of Galilee, why stand ye *gazing* up into heaven? —Acts i, 11.
Syn.—gape, stare.—To *gaze* is to look with fixed and prolonged attention, awakened by excited interest or elevated emotion; to *gape* is to look fixedly with feelings of ignorant wonder; to *stare* is to look fixedly with wide-open eyes, as in surprise or curiosity.

gāze, *v.t.* to look at intently. [Poet.]

gāze, *n.* 1. a fixed look; a look of eagerness, wonder, or admiration; a continued look of attention.
With secret *gaze*
Or open admiration him behold.—Milton.
2. the object gazed on; that which causes one to gaze. [Poet.]
at gaze; (a) in stag hunting, in the position assumed by a stag when becoming aware that the dogs are in chase; (b) at bay; in heraldry, having the head turned so as to look out from the shield: chiefly used in reference to the figures of a buck, hart, hind, or stag.


STAG AT GAZE

gā-zĕ'bō, *n.*; *pl.* **gā-zĕ'bōs, gā-zĕ'bŏes,** [humorously formed from *gaze*, and L. *-ebo*, a fut. ind. 1st pers. sing. ending of a second conjugation verb, meaning lit., I shall gaze.]
1. a summer house affording a fine view.
2. a turret or windowed balcony from which one can gaze at the surrounding scenery.

gāze'hound, *n.* a hound that pursues by sight rather than by scent.

gaz'el, ghaz'āl, *n.* 1. a piece of Arabic music with a frequent refrain.
2. a form of Persian verse.

Gă-zel'la, *n.* the type genus of gazelles: sometimes called *Dorcas*.

gă-zelle', gă-zel', *n.* [OFr. *gasel*, *gazel*; Ar. *ghazal*, *ghazel*, a gazelle.] a small, swift, graceful antelope of Africa, the Near East, and Asia, with spirally twisted, backward-pointing horns, and large, lustrous soft eyes; especially the *Gazella dorcas* of North Africa.


GAZELLES (*Gazella dorcas*)

Gaz-el-lĭf'nae, *n.pl.* a group of antelopes of which the gazelle is the type.

gaz'ĕr, *n.* one who gazes.

ga-zet', *n.* [It.] a copper coin formerly issued by the Venetian Republic. [Obs.]

ga-zette', *n.* [It. *gazzetta*, a gazette, newspaper, prob. from *gazzetta*, a gazet or small coin, the price paid for the paper; also thought to be from *gazzetta*, a magpie, and to mean a chatterer or tattler.]
1. a newspaper; a printed sheet of paper containing an account of current events: now used mainly in the names of some newspapers.

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of pharmaceutical and legal problems. The following definition of "a drug" is considered more suitable for this report:

> "A drug is any substance or product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient."

The term "new drug" has also been used extensively in this report. It is recognized that this term has legal or regulatory significance in some countries. It is not, however, used in that sense here but is only meant to imply that the drug has not been extensively investigated clinically.

3. BIOCHEMICAL STUDIES

The biochemical studies discussed in this section include absorption, distribution, excretion, and metabolism of a drug. Knowledge of these factors controlling drug action is of fundamental importance for proper evaluation of toxicity.

Typical experiments on new drugs involve the administration of single doses by various routes to animals and measurement of drug concentrations in body fluids and tissues. The purpose of these studies is to estimate the rate and degree of absorption, rate of disappearance from the body or body fluids, renal excretion and localization in tissues. In many instances, simple linear relationships can provide estimates of these and other parameters.

The value of quantitative studies of this type has been established. This information facilitates extrapolation of animal data to man, discloses metabolic products with therapeutic or toxic effects, and provides the rationale for development of suitable dosage regimens.

3.1 Method

The studies discussed here require methods for the assay of the drug in biological fluids and tissues. Most drugs can be assayed by a relatively few procedures such as spectrofluorescence, chemical coupling, ultraviolet absorption, and complex formation with dyes. For some drugs, the use of isotopic tracer methods may be necessary.

The specificity of the method must be known and may be established by techniques such as gas chromatography, thin layer chromatography, paper chromatography, and countercurrent distribution. In some instances, methods of low specificity may give useful information in

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Center for Drugs and Biologics
Food and Drug Administration
Department of Health and Human Services

GUIDELINE FOR THE FORMAT AND CONTENT OF THE NONCLINICAL PHARMACOLOGY/TOXICOLOGY SECTION OF AN APPLICATION

(These are NDA guidelines which are also applied to IND submissions. The page attached outlines the order of animal studies in terms of route of administration)

February 1987

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G. Route and Mode of Administration

1. Studies for each species within each type of study should first represent the intended route of human use, followed by data for other routes in the following relative order:

Oral
Intravenous
Intramuscular
Interperitoneal
Subcutaneous
Inhalation
Topical
Other in vivo
In vitro

H. Doses

1. Multidose data should be displayed from the lowest to the highest dose.

2. Within each multigroup study, results should similarly be presented in all tables in order of increasing dosage:

Untreated control
Vehicle control
Low dose
Middle dose(s)
High dose
Positive or comparative control(s)

3. Dose should preferably be based on the active moiety component if the drug is a salt or other dissociable derivative. In any case, it should be clearly stated that whether the calculation of dose is based on the active